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Agilent No. 10980096-1
R&A No. 5000-0051

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Patrick KALTENBACH et al.

Group Art Unit: 1743

Serial No.: 09/156,804

Examiner: P. Kathryn Bex

(Continued Prosecution Application)

Filing Date: September 17, 1998

Title: MODULAR APPARATUS FOR CHEMICAL
MICROANALYSIS

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
Washington, D.C. 20231

Sir:

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We, Patrick Kaltenbach and Tom Van de Goor, hereby declare as follows:

1. We are joint inventors of the subject matter described and claimed in the above-identified patent application.

2. Prior to September 15, 1998, we conceived of and reduced to practice the invention as set forth in the claims of the subject patent application, as originally submitted and as amended in the accompanying response filed concurrently herewith. That is, we conceived of and reduced to practice: a modular microchannel apparatus for the chemical analysis of an analyte in a sample as recited in claims 1-8, 10-12 and 26; a kit for making a modular

microchannel apparatus for the chemical analysis of an analyte in a sample as recited in claim 25; and a modular microdevice of analyte analysis as recited in claims 28-30.

3. Evidence that we reduced the invention to practice is provided in accompanying Appendix (I), which includes pages 60-79 from Dr. Van de Goor's notebook 2559. All dates deleted from the pages in Appendix (I) are prior to September 15, 1998. Page 69 is noteworthy since it contains a schematic illustration of the claimed device. In addition, on page 72, a handwritten entry provides evidence that a chip in a cassette was tested. Experimental data in the form of current electropherograms are provided on pages 73 and 74. E-mail communications relating to temperature control are provided on pages 75 and 76. Further experimental data in the form of additional current electropherograms are provided on pages 77-79. Thus, we the invention was reduced to practice before September 15, 1998, i.e., prior to the filing date of U.S. Patent No. 6,103,199 to Bjornson et al.

We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: _____

Patrick KALTENBACH

Date: July 23, 2001


Tom VAN DE GOOR



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R&A No. 5000-0051
U.S. Ser. No. 09/156,804

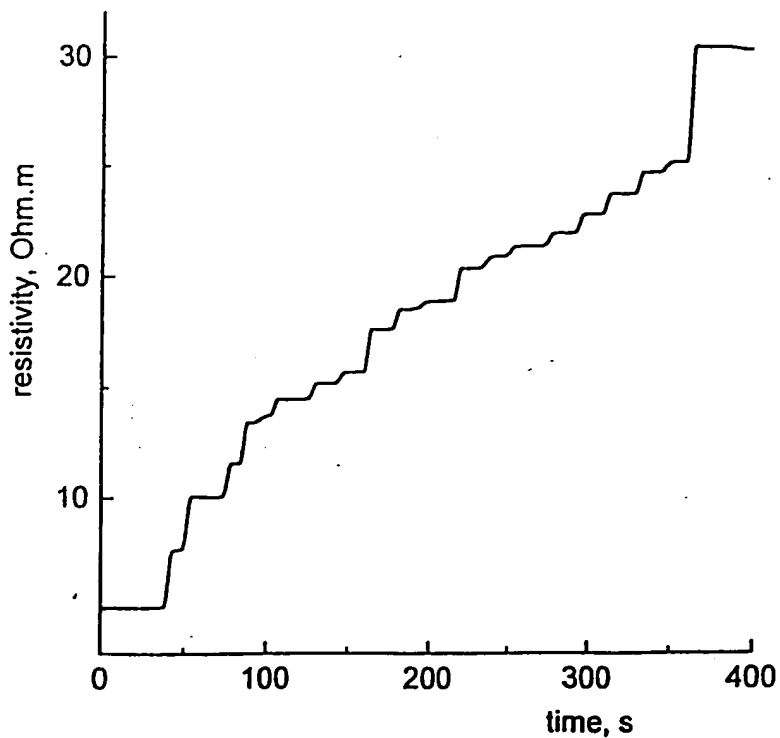
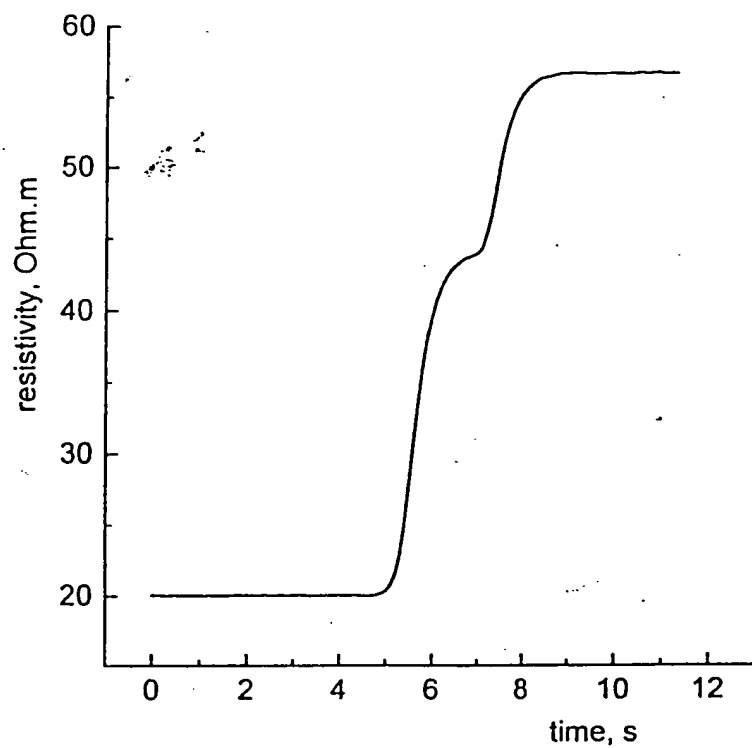
APPENDIX I

Pages 60–79 from Dr. Van de Goor's Notebook No. 2559.

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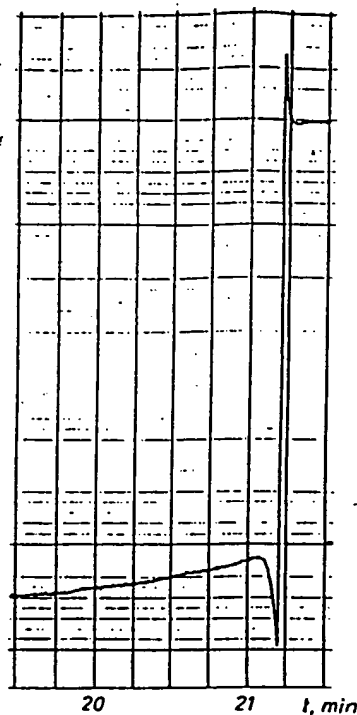
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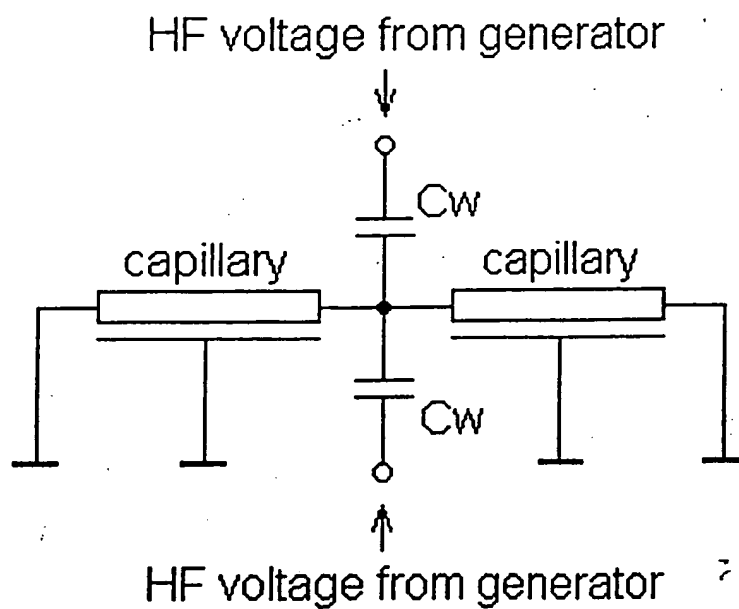
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Problem of "anomalies"



Explanation and solution to the problem



Signed *Samraf*

B. Wedberg

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Producer of HFCLD for isotachophoresis:

Dr. Marian Koval
Villa-Labeco s.r.o.
Chrapčiakova 1
SK-052 01 Spišská Nová Ves
Slovakia

tel. +421 965 42 60 32

fax +421 965 42 60 30

3 Different solutions were flushed through the system and the signal at 4.19 MHz recorded.

Solution 1: 100 mM KCL

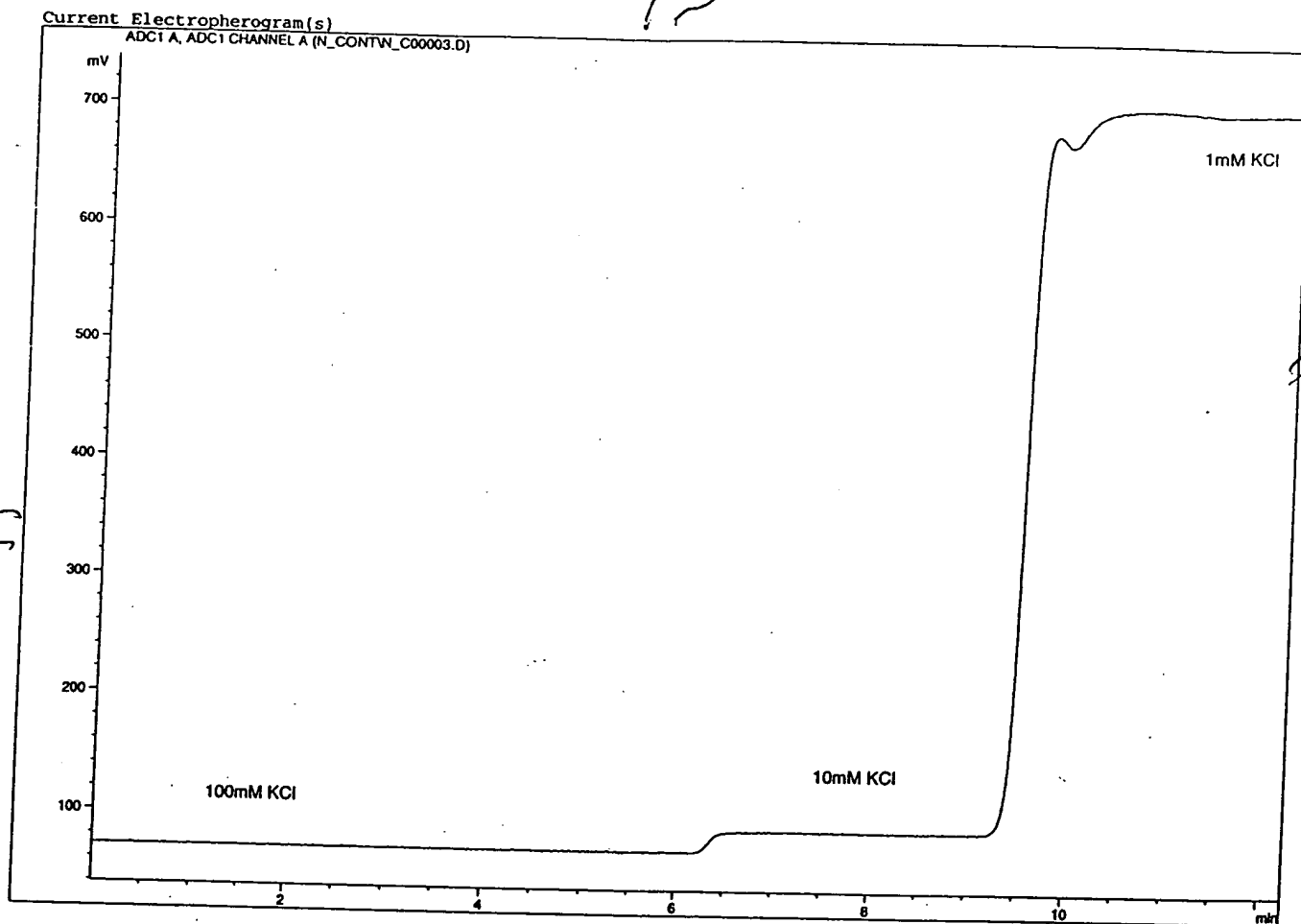
Solution 2: 10 mM KCl

Solution 3: 1 mM KCL

As is clear from the signal there is a very non-linear response to these different concentrations.

The step from 100 to 10 mM is very small while the step from 10 to 1 mM is very large, almost over the full scale of the detector.

This is also clear from the transfer function curves. For the most sensitive detection a background electrolyte concentration around 1-3 mM KCL would be ideal.



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To demonstrate this fact two different experiments were performed.

In the first case a typical CE background buffer of 10 mM borate at pH 9.3 was prepared and was spiked with 0.5 mM KCL and 5 mM KCL respectively.

In the other case a background electrolyte of 1 mM borate buffer was spiked 10 uM, 50 uM and 500 uM respectively.

In the first case the background conductivity was such that the measurements were not in the most sensitive part of the response curve. 0.5 mM could just barely be detected and even 5 mM gave only a limited signal.

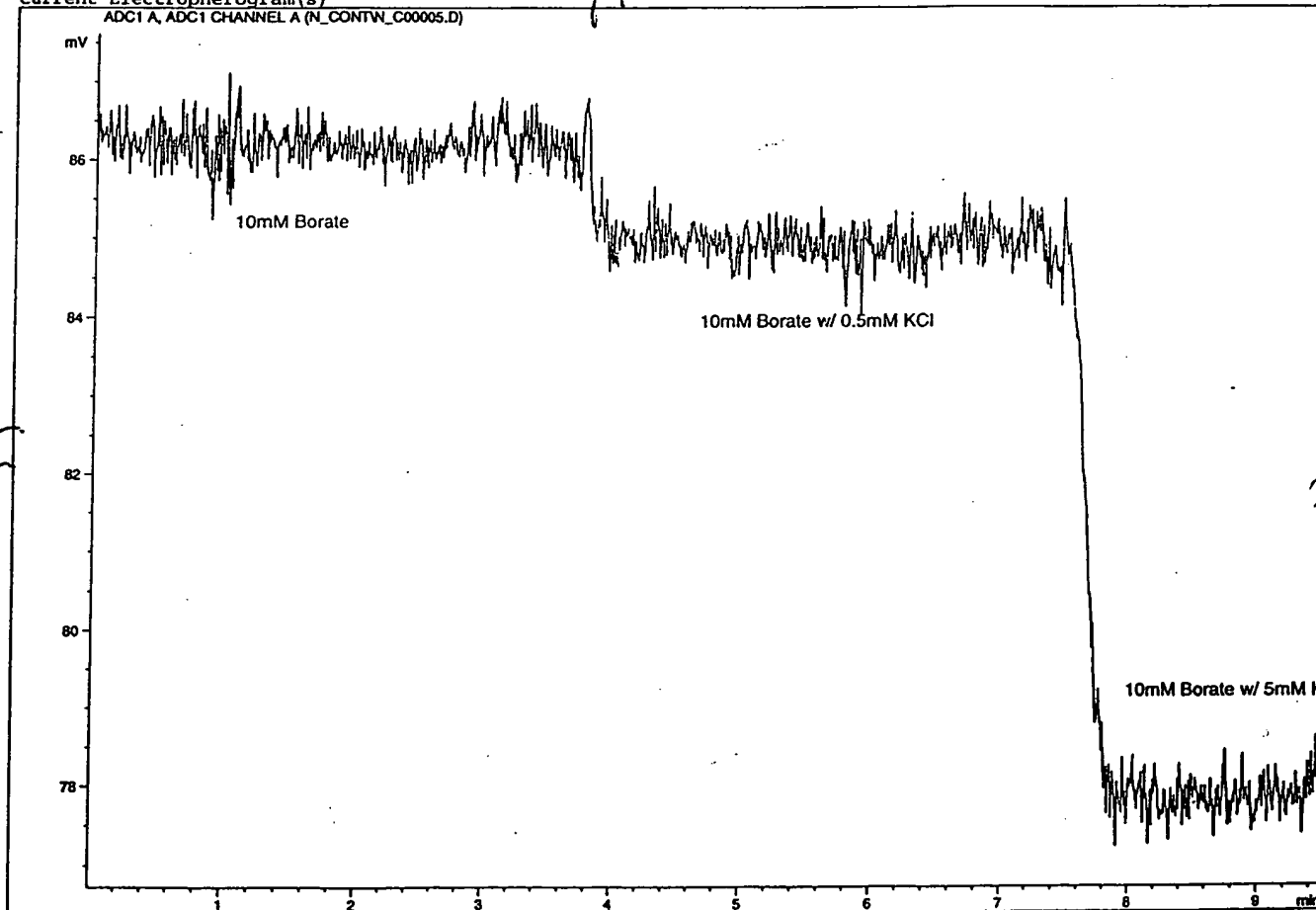
In the other case however, 0.5 mM or 500 uM give a huge signal while even 10 uM could be detected.

This again expresses the need for matching of measuring frequency to background conductivity. It also could be important to have detection at multiple frequency if high sensitivity over a wider conductivity range is required. Simple multiplexing of the frequency could do that.

The detection limit of 10 uM puts this simple experiment right in the range that is achievable with indirect UV detection for small ions that cannot be measured using direct absorbance. Therefore this approach could be very useful in the field of ion analysis.

Current Electropherogram(s)

ADC1 A, ADC1 CHANNEL A (N_CONTW_C00005.D)

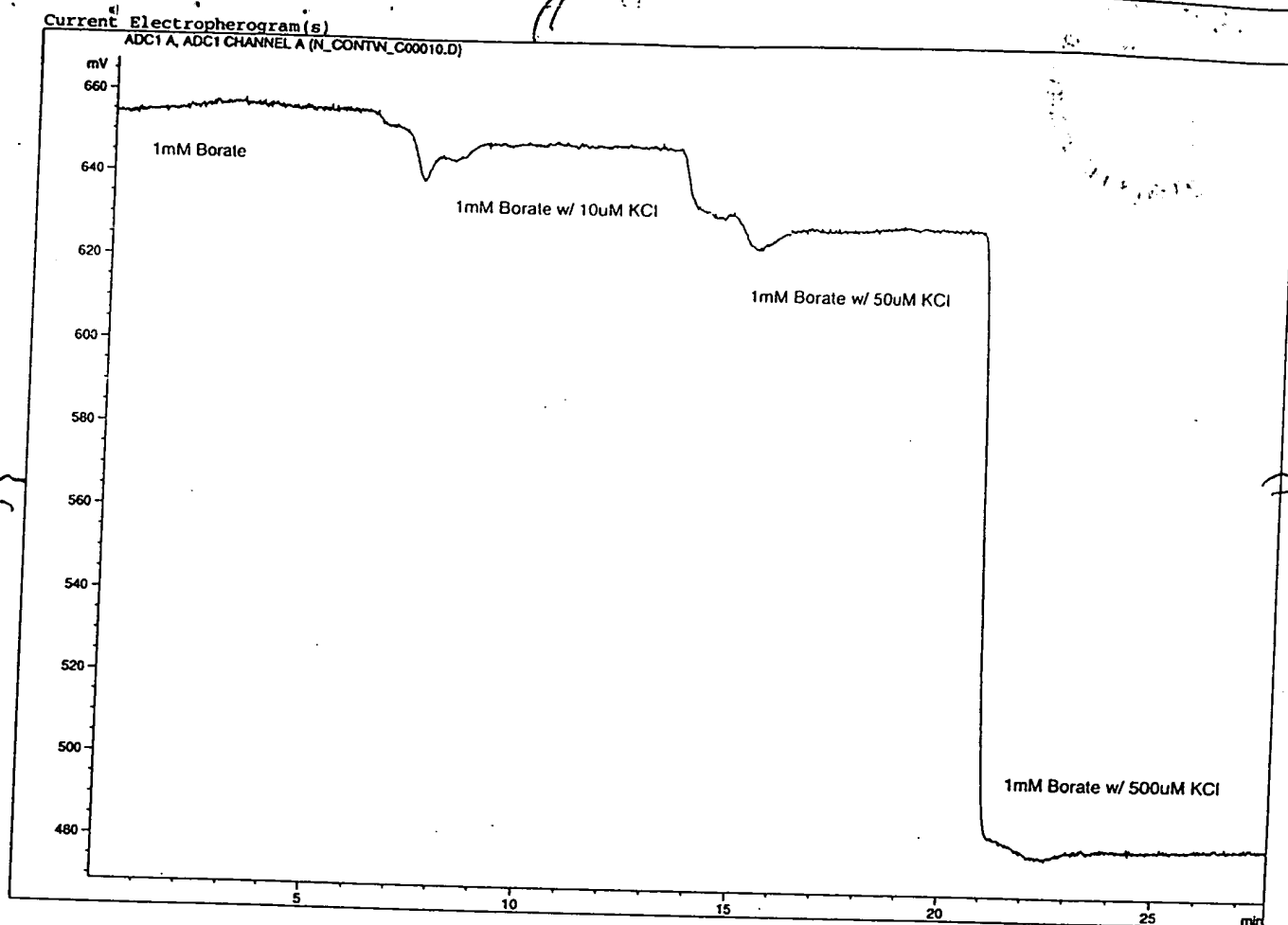


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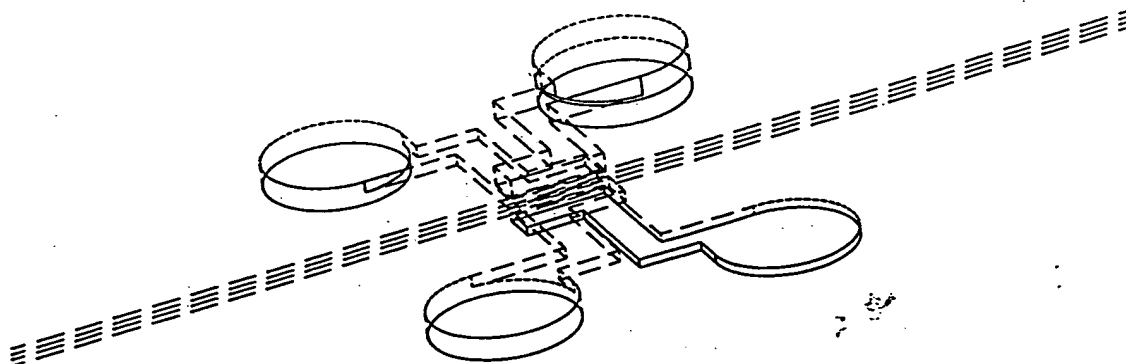
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Page 1 c

Reducing dimensions by using microstructures and optimized signal electronics could further enhance sensitivity.
The following ablated structure was proposed as a didjet, to test out this concept



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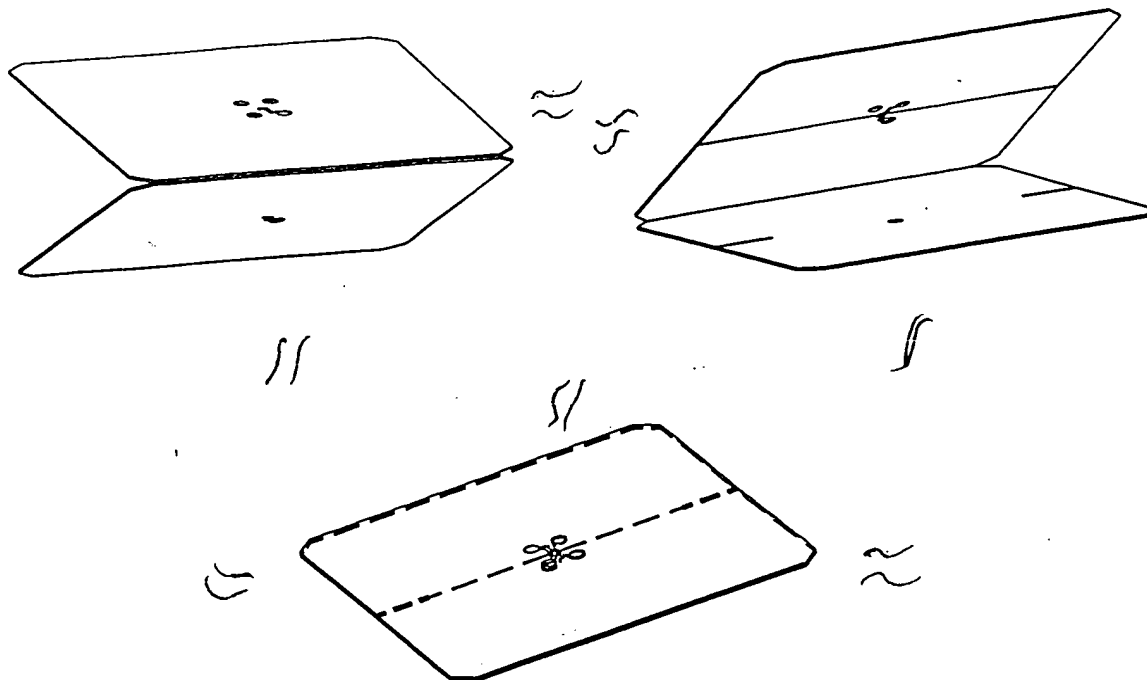
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The didjet consists of a channel with connectors for tubing like in the case of the optical didjets. In addition to that is ahas ablated antenna areas on each of the sides of the channel (up, down, front and back) connected to pads where contact can be made. The structure is made by ablation of a sheet with a single fold by ablation on both sides. Pins used in printed circuit board testers that have little springs can be used to contact to these pads. The metal contact in the structure is made by placing 60 um thin nikkel pieces inside the structure after which it is folded and heat staked. By placing either two or four of these antennae inside the structure the previous two approaches could be tested and compared.



This approach could then be part of a more integrated structure where one would have on device conductivity detection for e.g. ion analysis. One approach to such custom chip is shown below and could be used for ion analysis using a column coupled system. The first section could be used for preseparation, while the second section is the analytical separation. When this would be ran in ITP/ITP or ITP/CE mode, specific ions could be stacked and analyzed and switching be done based on conductivity.

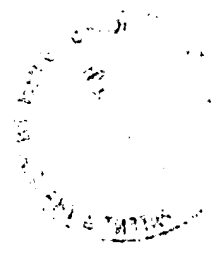
Since in ITP mode specific ions migrate in zones with specific conductivity, depending on the choice and concentration of the leading ion, one can set the conductivity detector at the bifurcation point such that some ions are moved to waste while others are allowed to enter the analytical separation channel. This method is common in ITP and can be found extensively in reviews like: Isotachopheresis, theory, instrumentation and applications by Everaerts, Verheggen and Bekkers, Elsevier, 1976.

In this way low levels of ions can be detected in the presence of large amounts of others by not allowing the unwanted ions to enter the analytical column. The following two pages show schematically the filling and switching in such a device. In red is shown the leading electrolyte, in blue the trailing electrolyte which also serves as background electrolyte in the zone electrophoretic portion and in black the sample band. In this case a simple Z-injector is used and two integrated conductivity detectors are shown. The first one at the switching point and the other at the end of the separation channel.

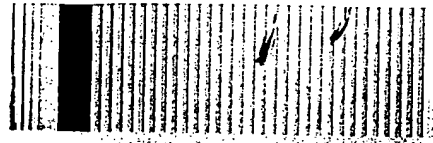
Integrated conductivity detection and the use of ITP would lead to a much smaller instrument packages since there are no large components due to the detector and the required power supply could be much smaller for ITP analysis. (Typical less than 10 kV)

Revised

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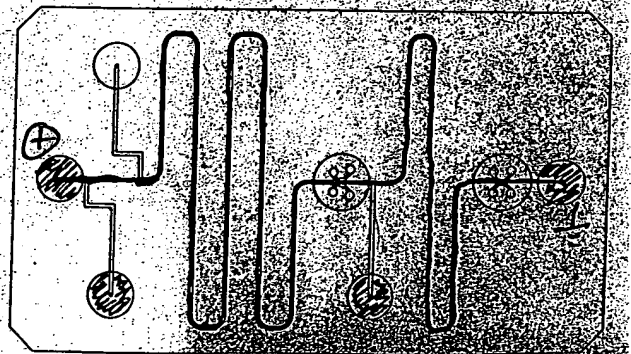
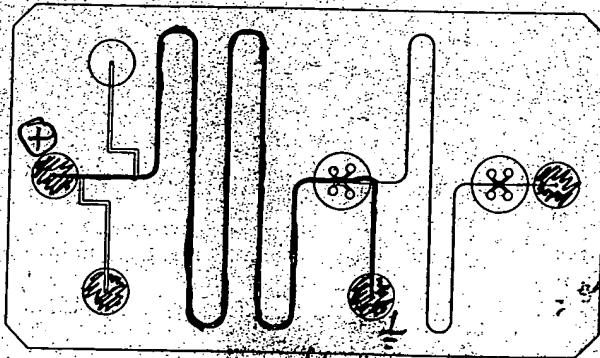
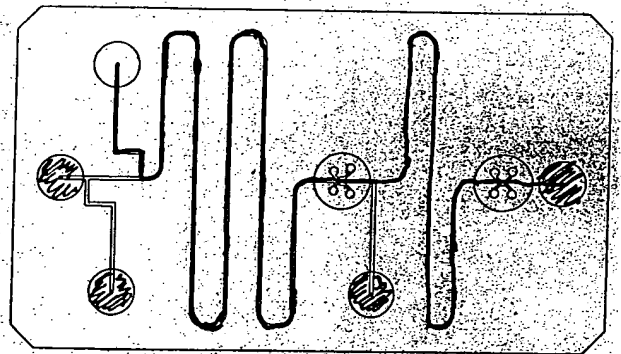
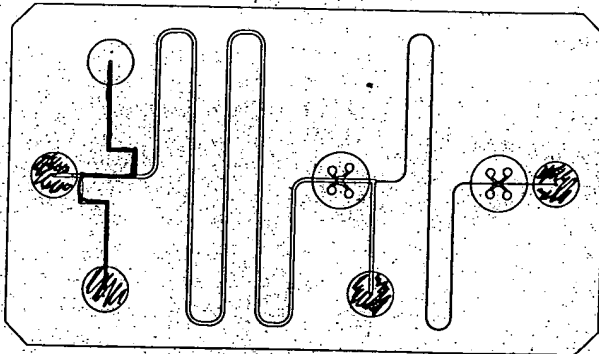
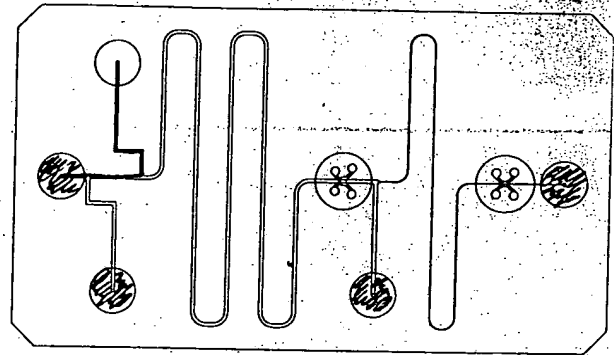
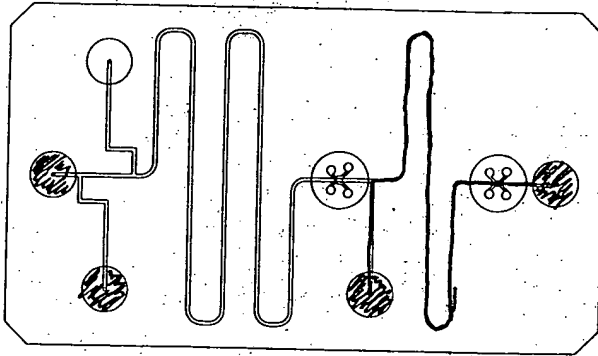


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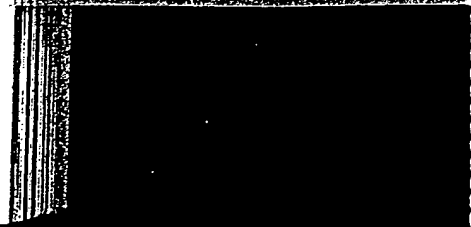
ITP/ITP



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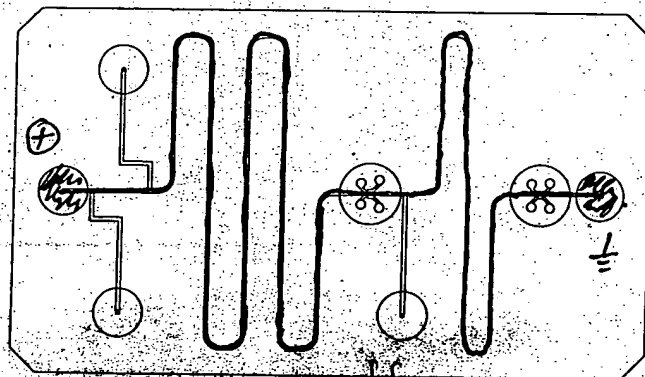
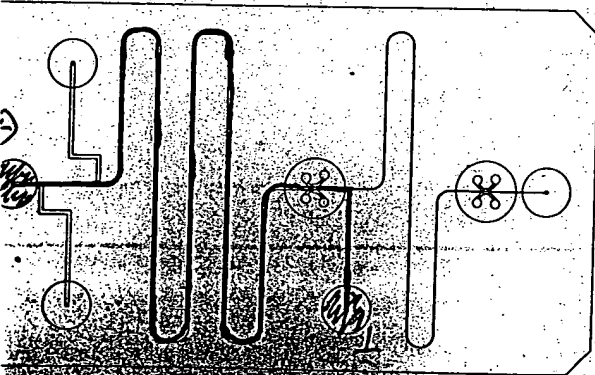
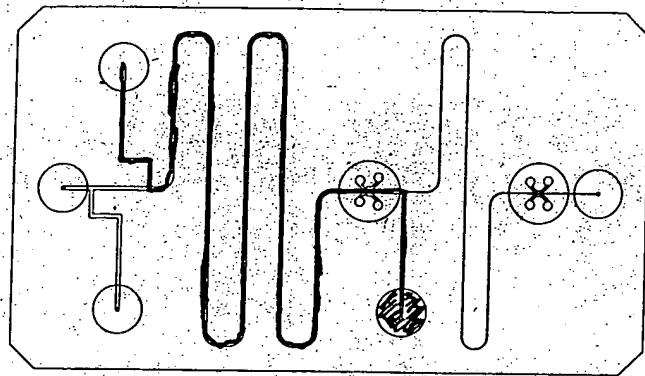
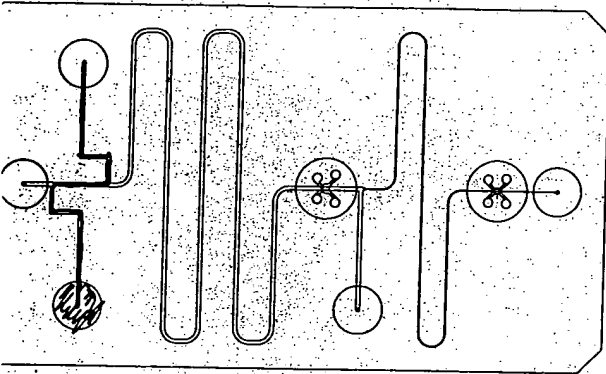
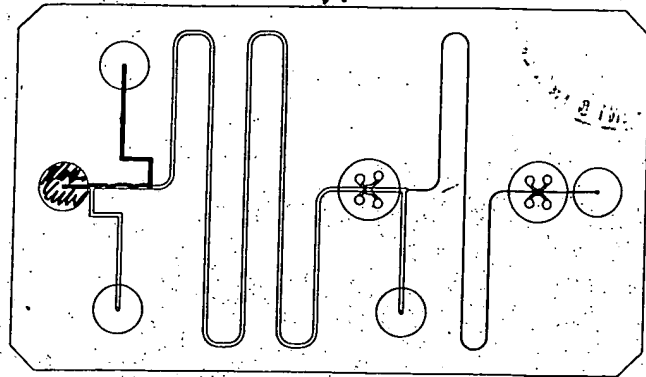
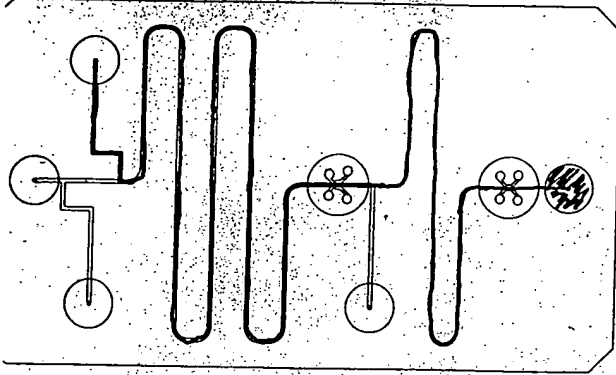
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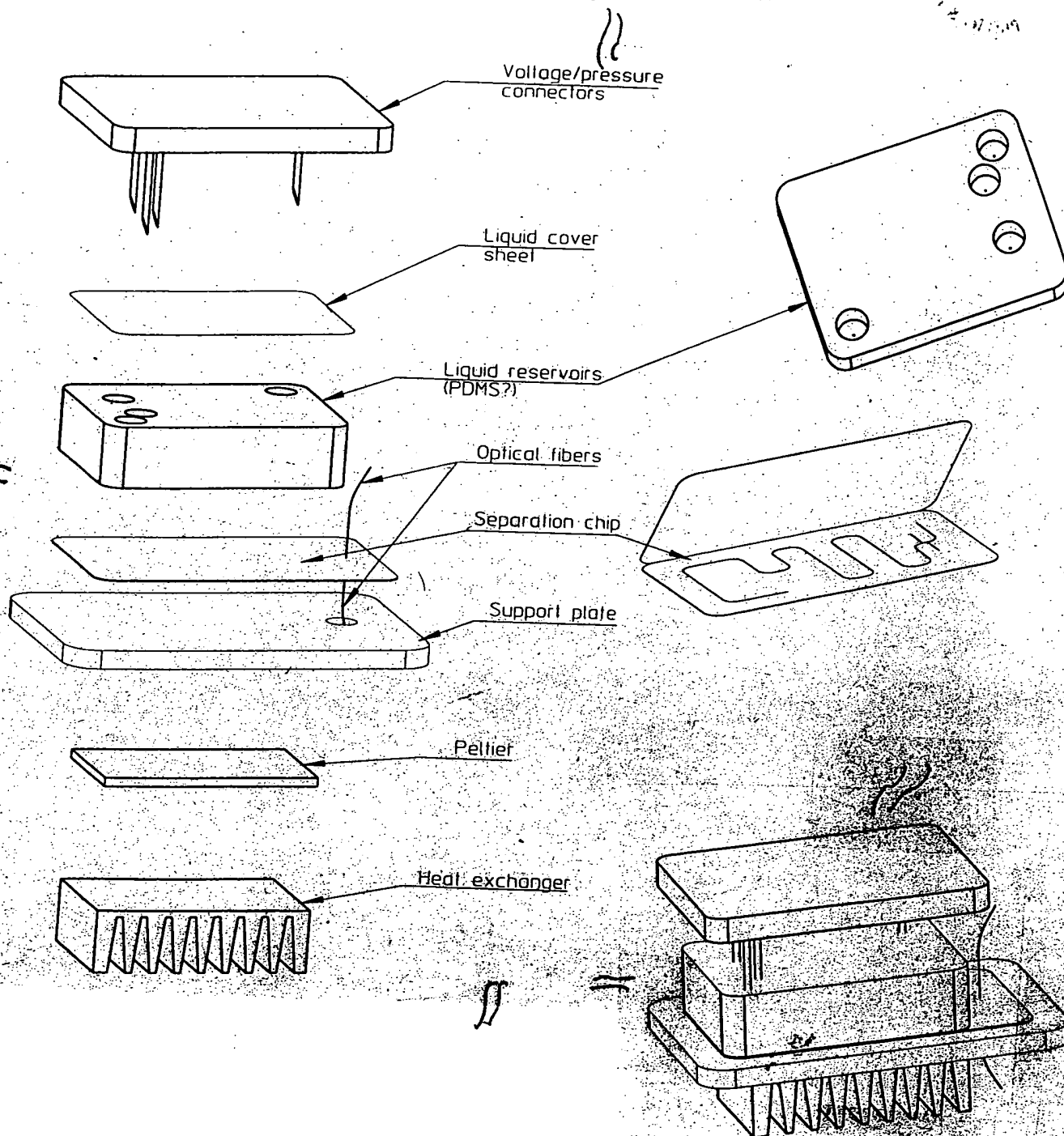
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The interface between the chip and the buffer reservoirs could be accomplished using a two-stack chip approach. In this approach two chips are stacked together. One of them is the separation chip, the other a liquid handling chip, containing all the buffers, and reagents. An interesting approach would be when the liquid handling chip would be made of a silicon like material, which could therefore seal by means of pressure onto the other (separation) chip.

This would lead to a stack shown in the picture below that would built-up the entire instrument.



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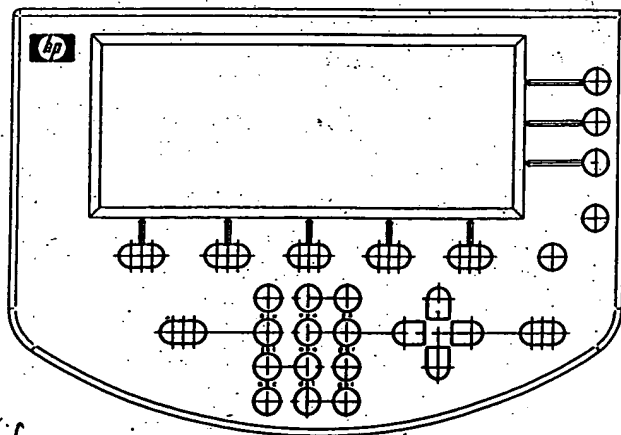
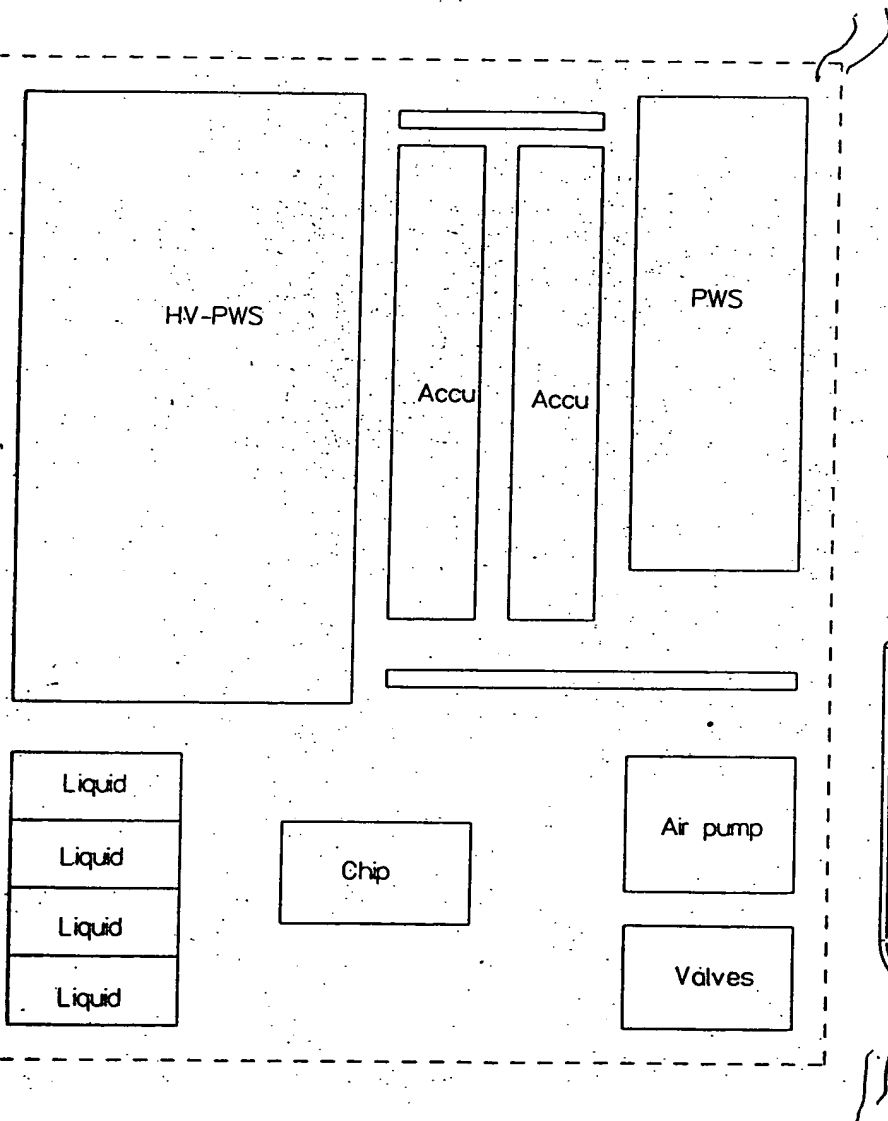
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This would cut down on the overall footprint of an instrument. The image below shows schematically the layout of a portable ion analyzer. Based on the power consumption calculation, it could run on two batteries from a notebook computer. Instrument control could be done using the Da Vinci controller, drawn on size.



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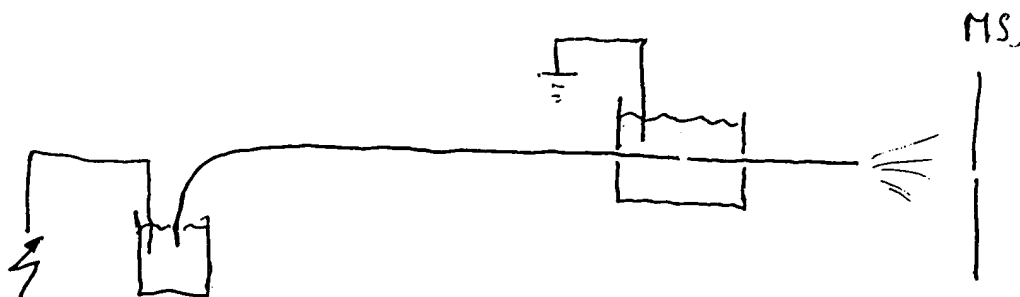
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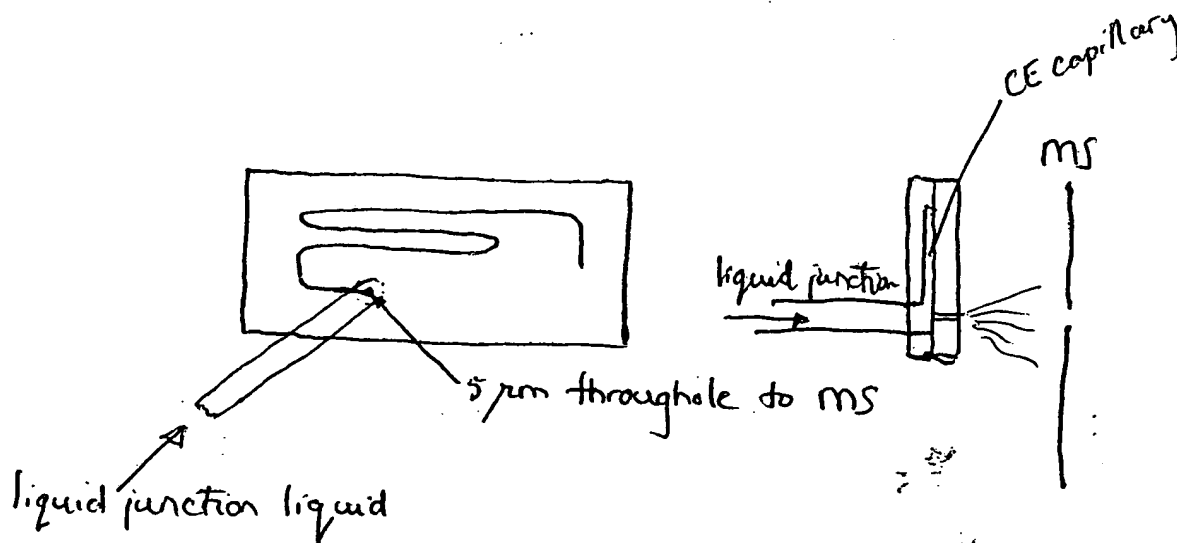
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To do an electrospray mass-spec coupling to chip, a liquid junction interface is one of the options. In this approach in the case of CE-MS the CE capillary is brought in extreme close contact to a spray/transfer capillary, such that electrical contact can be made and that make-up liquid is allowed to enter the transfer capillary, without significant loss of sample coming out of the CE column. Very precise positioning is in this case critical.

The preferred way of doing this is trying to keep the transfer capillary very short and the i.d. of this capillary very small in order to efficiently transfer the sample to the spray tip. Especially for micro spray or nano spray applications these dimensions are very important. The figure below shows schematically this setup.



In the chip situation a similar implementation could be used, with the additional advantage that precise positioning could be done by microfabrication and connectors could be made in three dimensions. One example is shown below. In this approach the regular chip outlet is used as the liquid junction line. A small hole is drilled through to the back side of the chip. This hole could be 5-10 μm in size and be used to spray from. This could be directly of chip or a little tip could be attached. In that case voltage could be applied at the tip. It could also be supplied through the liquid junction line or a small metallized contact or wire could be integrated in the chip. By making the liquid junction line large with respect to the separation channel, one can prevent a pressure drop across the separation compartment.



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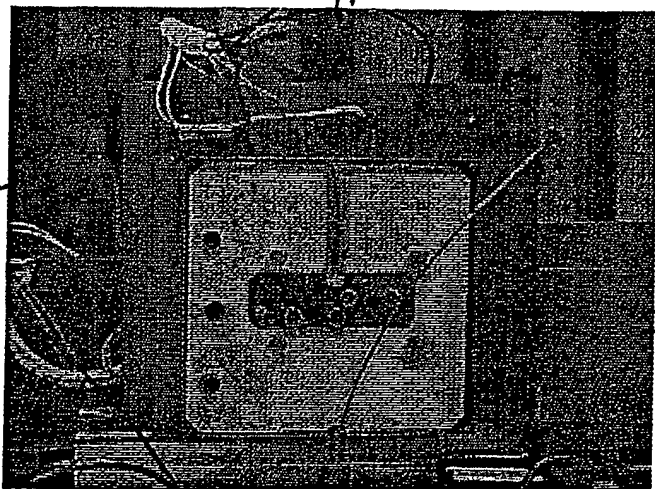
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Thermostating of the chip in the cassette was retested after a new ceramic backplate came back from the model shop.

The plate covers the full area of the copper cooling plate to prevent arcing as experienced in previous experiments at higher voltages ($> 15 \text{ kV}$).

The alignment pins don't go through the plate as to not to touch the copper part. Moreover pins are now made of a polymer material so they do not conduct electrically.

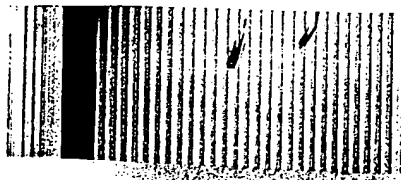
The ceramic plate is a trade-off between electrical insulation and heat conductance. Thickness of the plate is about 1 mm.



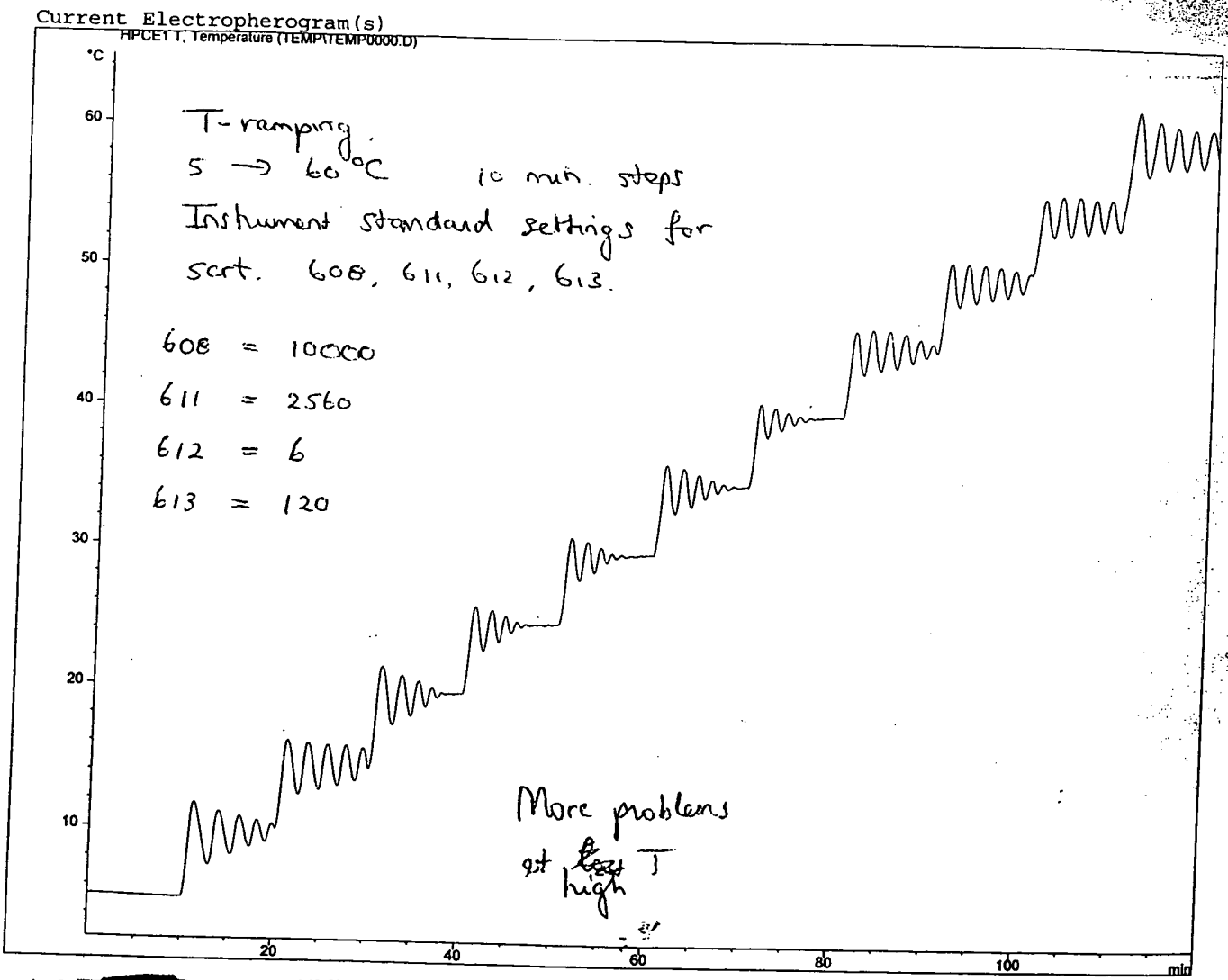
Chip in thermostatted cassette



2559- 73



Print of window 38: Current Electropherogram(s)



Instrument 1 [REDACTED]

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Date [REDACTED] Signed [REDACTED] Date [REDACTED]



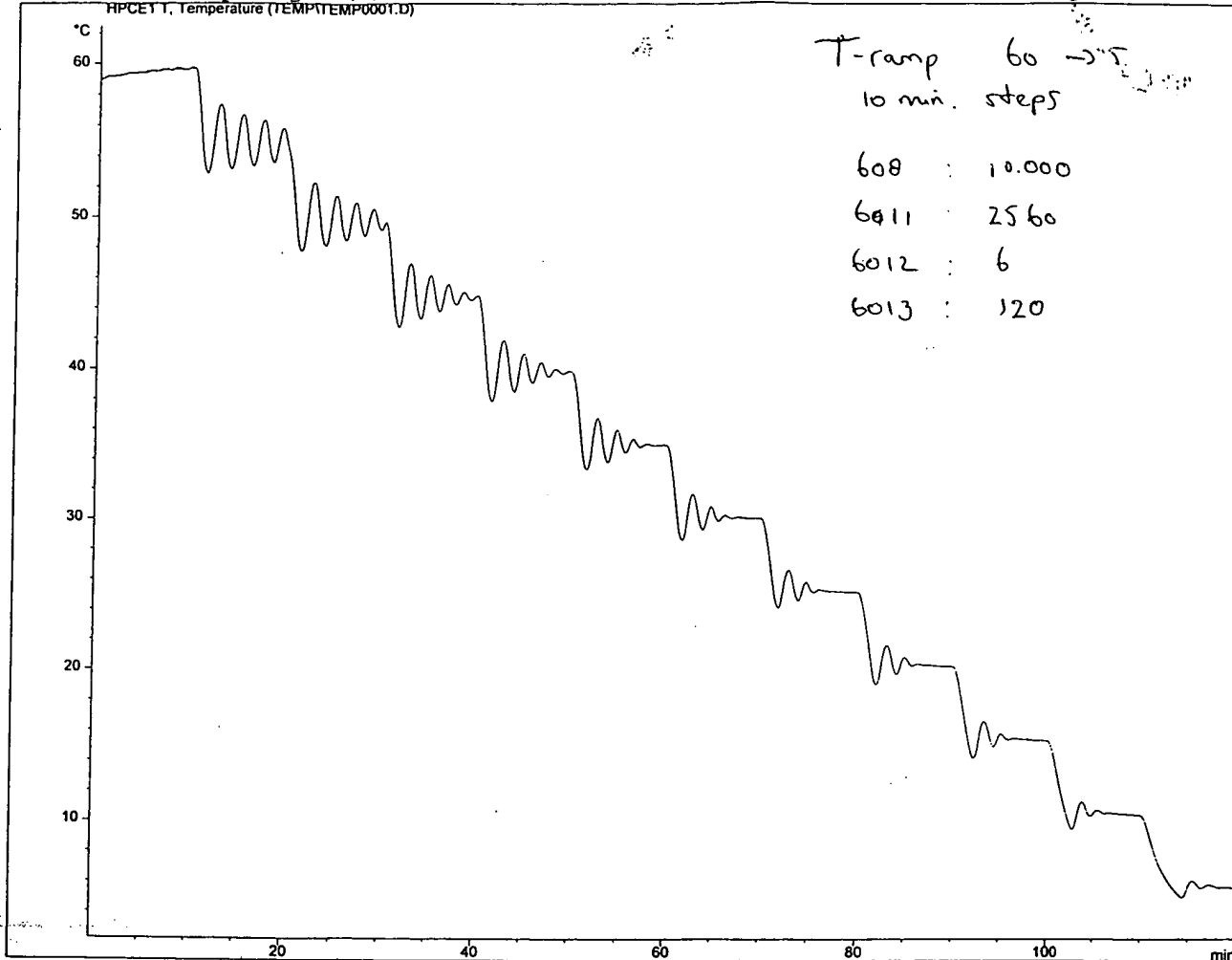
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Print of window 38: Current Electropherogram(s)

Current Electropherogram(s)

HPCE11, Temperature (TEMP1TEMP0001.D)



Instrument 1 [REDACTED] tom

Page 1 of 1

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[REDACTED]



FRITZ BEK@HP-Germany/om20

To: Tom vandeGoor/Labs/HP/US@HP, KLAUS WITT@HP-Germany/om18@BOI-GW1
cc: FRITZ BEK@HP-Germany/om20@BOI-GW1
Subject:

Hello Tom,

I looked into the code for temperature control of the CE and wrote down the secret commands you need to control your peltier with our controller. You should connect our three temperature sensors for peltier hot side, peltier cold side (that's in our notation the side of the peltier we use for cooling the instrument) and ambient temperature with your peltier (connect the ambient temperature sensor and the peltier cold side sensor with the same side of your peltier).

The commands are :

schr -608,<value>,0	value sets the maximum allowed Power (10000 = 5.2 Ampere)
schr -611,<value>,0	value sets the P-Factor (1600 = 5.2 Amp at a dT of 6.25 C)
schr -612,<value>,0	value sets the I-Factor (Tn[sec] = I-Factor*3)
schr -613,<value>,0	value sets the D-Factor

I would start with a max Power-setting according to your peltier and with a pure P-controller. Set I-Factor and D-Factor to 0. Start with a P-Factor of 1600 and increase it until the controller becomes unstable. Then decrease it 30%. Then start with an I-Factor of 5. If the system becomes unstable increase it.
I think you don't need the D-part.

kind regards

Fritz
When this

Systems locks up
when 613 is set to 0.

Continued on Page

Read and Understood By

Signed

Date

2559- 76

Hewlett-Packard Laboratories

Approved for Release

FRITZ BEK@

To: Tom vandeGoor/Labs/HP/US@HP
cc: FRITZ BEK@HP-Germany/om20@BOI-GW1, KLAUS WITT@HP-Germany/om18@BOI-GW1,
HONGFENG YIN@HP-PaloAlto/om8@BOI-GW1
Subject: Re: thermostating

Hello Tom,

I tried the secret commands on my instrument. When I set the D or I-Value to 0 my instrument locks up, other values are ok. To disable the I-Value and the D-Value you have to set it to a high value, not to 0.

The listing of the current P-value works with the following command
hpiB "scrt 611,0,0"

in the reply you find the actual value.

I would try to use a higher power setting and a higher P-Factor.

Start with:

hpiB "scrt -611,1000,0"

hpiB "scrt -612,2000,0"

hpiB "scrt -613,2000,0"

this sets your P-Value to 1000 and disables your I and D-Value nearly

regards

Fritz

>

> Hello Fritz,

>

> Once again thanks a lot for your help.

> We downloaded the new firmware into the instrument and tried again the

> secret commands.

> We are able to set the maximum power and the P-value.

> However when we try to set the I-value or the D-value, the instrument

> returns an error, but without anything in the logbook.

> When we try to reset the instrument after this error message, the machine

> locks up and we have to reboot.

> When just using the P value, we were able to do some thermostating on the

> mock-up cassette.

> The response with a P-value of 32 and a temperature set value of 25 C,

> resulted in a sinus-wave like response around 25 with a magnitude of 0.3 C

> and a repeat rate of about 1 cycle per minute.

> When we repeated this experiment, it was much more stable within 0.1 C.

> With this low power setting we could not get the temperature over 28.5 C,

> but with higher power the stability will probably be worse.

> Any advice?

> Another questions concerns the return value after the secret command in

> order to find what the current value is.

> secret "608,0,0" does not return the present value.

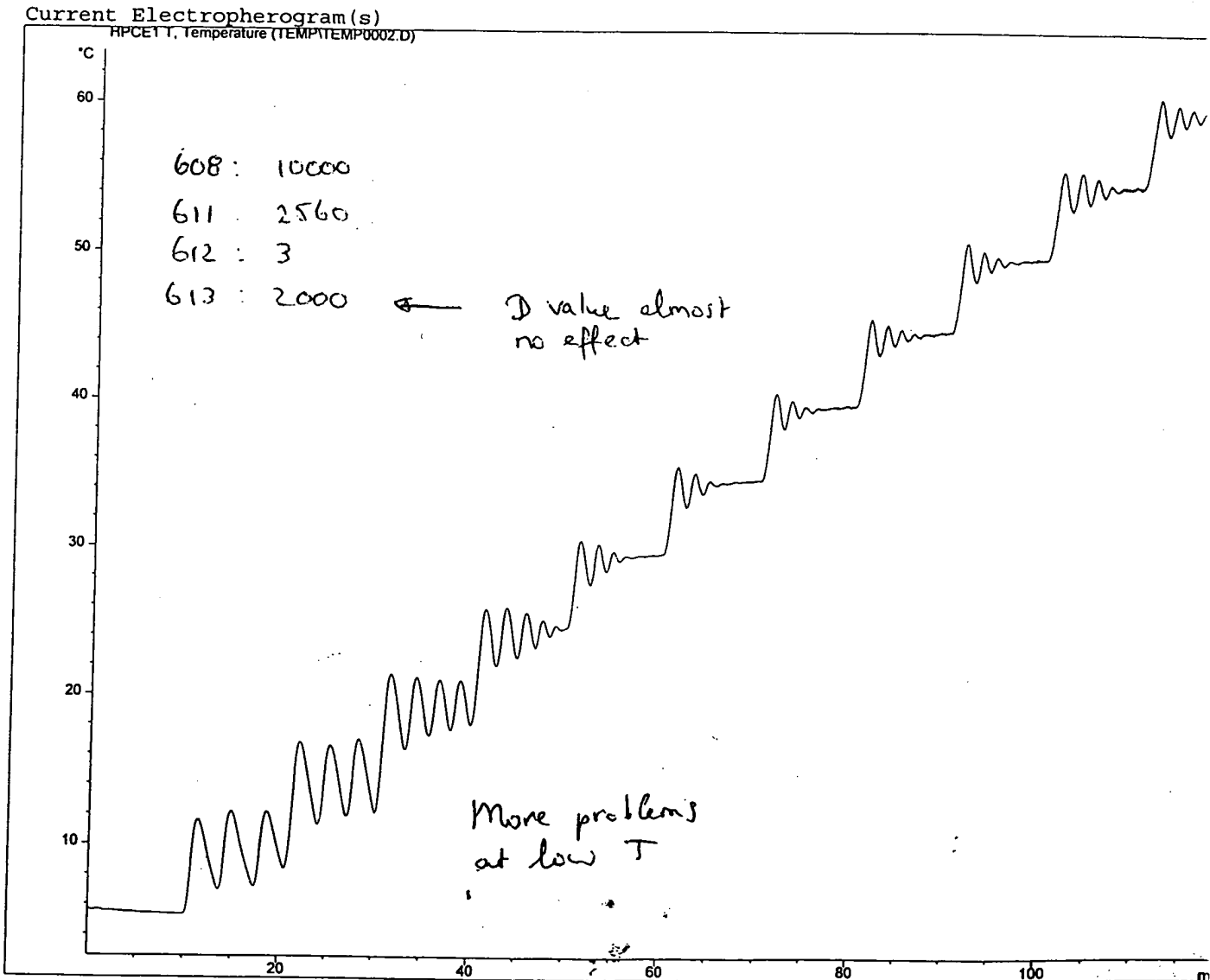
> Is there anyway around that?

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Print of window 38: Current Electropherogram(s)



Instrument 1 [REDACTED] PR tom

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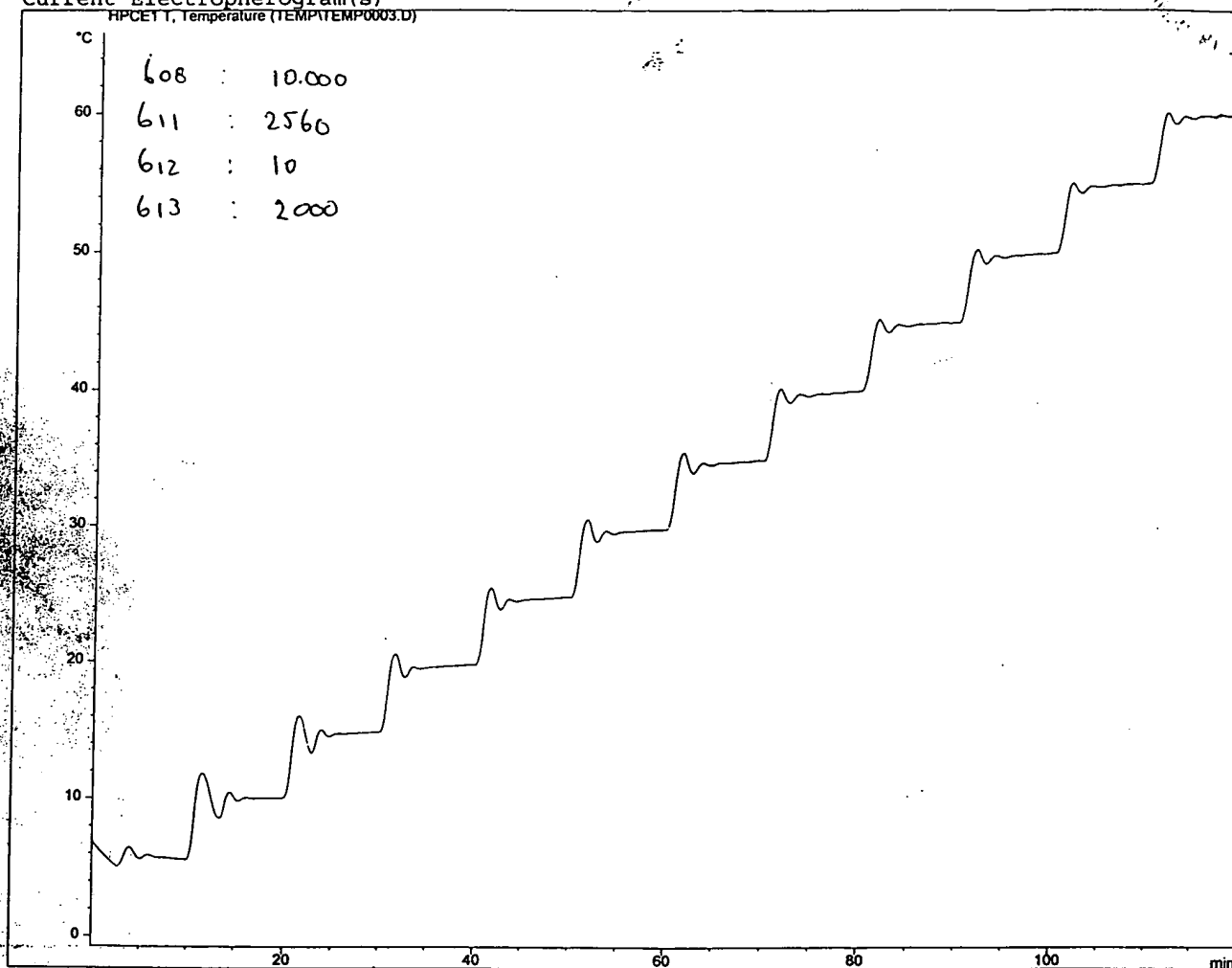
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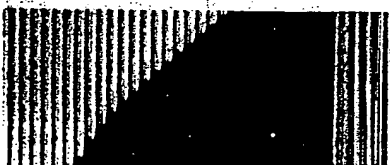
Current Electropherogram(s)

HPCE11.T, Temperature (TEMP\TEMP0003.D)



Instrument 1 [REDACTED].com

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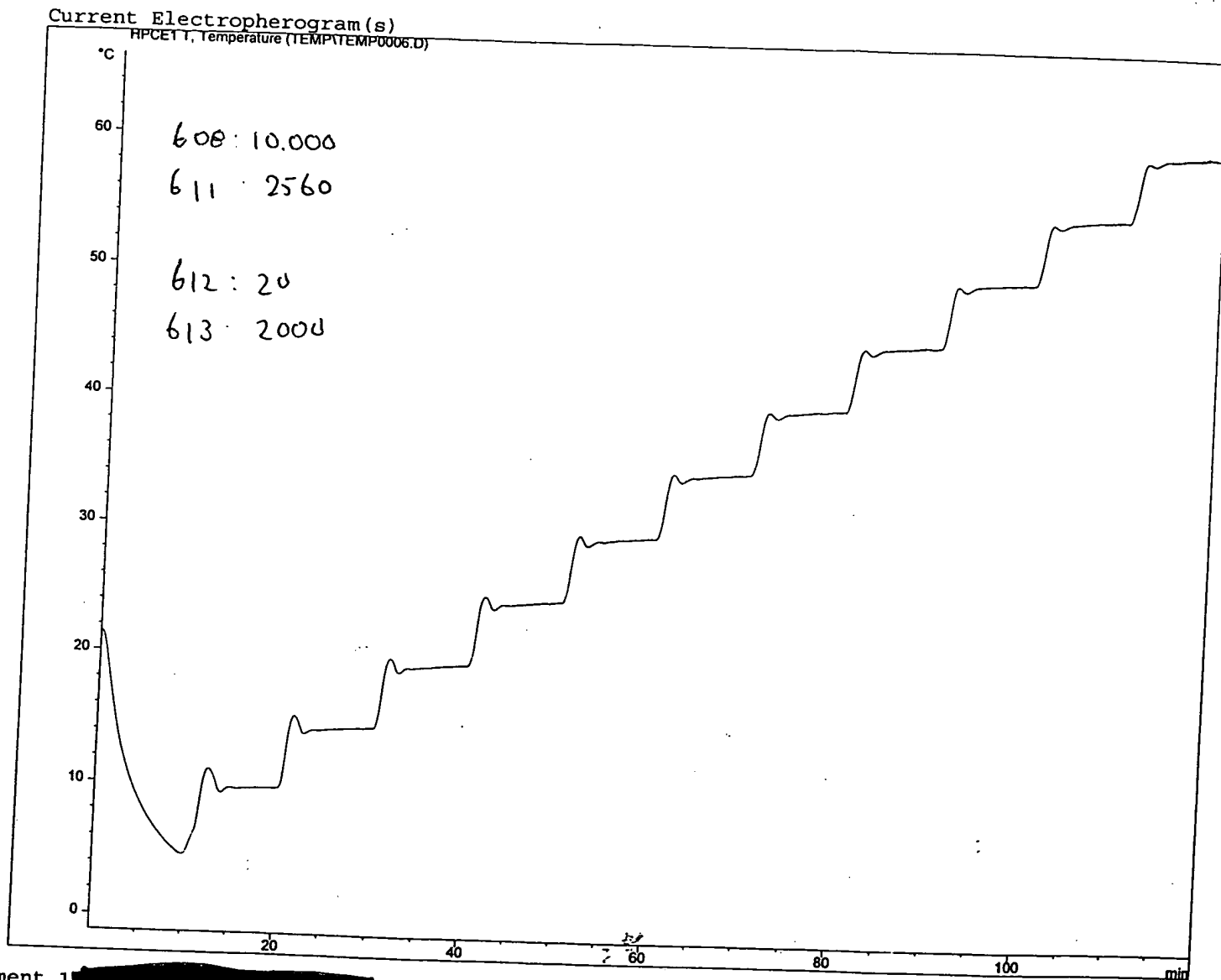
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Print of window 38: Current Electropherogram(s)



Instrument 1 [REDACTED]

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